The Synthesis of 1-Alkyl-4a-(4-chlorophenyl)-4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-one

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The primary amino group of 3-(2-aminoethyl)-3-(4-chlorophenyl)-2,3-dihydro-1*H*-isoindol-1-one (**1**) was acylated with acetyl chloride, benzoyl chloride and phenyl acetyl chloride to form the amides **2a-c**, respectively. These were cyclized in phosphorus oxychloride to give the 1-substituted-4a-(4-chlorophenyl)-4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-ones **3a-c**. Heating of **1** in formic acid lead to the formation of 4a-(4-chlorophenyl)-4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-one (**3d**). Heating of **1** in the presence of phosgene lead to the formation of 4a-(4-chlorophenyl)-2,3,4,4a-tetrahydropyrimido[6,1-*a*]isoindole-1,9-dione (**4**).

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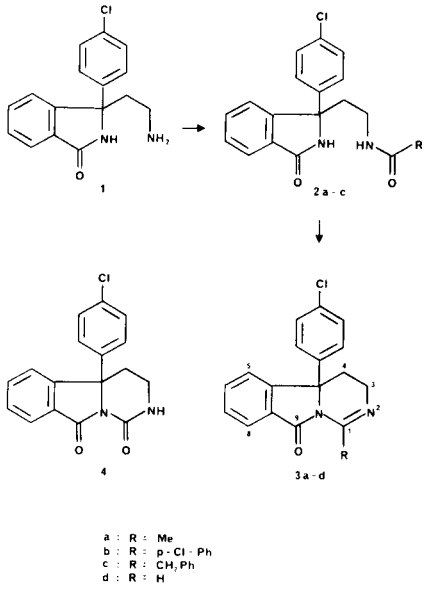
We have reported the rearrangement [2] of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindoline to 1-amino-4-phenylphthalazine in the presence of hydrazine. The carbanion prepared from the same isoindoline in the presence of sodium hydride underwent reactions with alkylating agents such as alkyl halides [3], phenacyl bromide [4] and methyl chloroacetate [4], respectively. We also have recently described the preparation and stereochemistry of 1-substituted-4a-(4-chlorophenyl)-2,3,4,4a-tetrahydropyrimido[6,1-*a*]isoindol-9(1*H*)-ones [5]. These were prepared starting with the cyanomethylation of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindoline to give the amine **1** in three steps. We now describe the acylation of this amine and its subsequent cyclization to a variety of novel 4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-ones. To date only one paper has been published [6] referring to this ring system and this described compounds of different oxidation stage with different substitution patterns.

Scheme 1



The primary amine **1** was acetylated with acetyl chloride in the presence of sodium hydroxide in a two phase system. When the resulting acetate **2a** was heated in refluxing (106°) phosphorus oxychloride for five hours cyclization to the pyrimido[6,1-*a*]isoindolone (**3a**) was accomplished in 34% yield. The proposed structure is in agreement with the analytical data presented in the experimental section. The upfield shift of the signals observed for one of the protons associated with the two methylene groups is in agreement with a cyclic structure. These signals are assigned [5] to the axial proton on C4. Acylation of the primary amine **1** with *p*-chlorobenzoyl chloride led to the amide **2b** in 74% yield. Cyclization of this compound to **3b** was accomplished in refluxing phosphorous oxychloride in 38% yield after one recrystallization. As was observed above, the signal for the axial proton on C4 in the nmr spectrum of **3b** was shifted upfield with respect to the other three protons of the two methylene groups.

Acylation of the primary amine **1** with phenylacetyl chloride led to the amide **2c** in 83% yield. In refluxing phosphorous oxychloride cyclization to **3c** was accomplished in 38%. Again the nmr signal for the axial proton on C4 appeared shifted to higher field in agreement with a cyclic structure **3c**. Also the signals for the two benzylic protons appeared as two doublets indicating restricted rotation of the benzyl group due to steric hinderance. Heating the free amine **1** in refluxing formic acid for 72 hours resulted in the formation of the cyclic compound **3d** in 34% yield. In the nmr spectrum a consistant shift to higher field of the signal attributed to the axial proton on C4 was observed. The free amine **1** was also heated in the presence of phosgene to form the cyclic urea **4** in 20% yield. The signal for one of the protons on C4 in the nmr spectrum of **4** appeared shifted upfield by 1 ppm.

EXPERIMENTAL

Proton magnetic resonance spectra were obtained on a JEOL FX 200 spectrometer and are recorded in Hertz or δ values (parts per million)

relative to TMS (tetramethylsilane) as internal standard. Infrared spectra were recorded on an Analect Instrument FX-6200 FTIR. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG. Mass spectra were measured on a LKB 9000 (low resolution).

N-{2-[1-(4-Chlorophenyl)-2,3-dihydro-3-oxo-1*H*-isoindol-1-yl]ethyl}-acetamide (**2a**).

Prepared from 6.4 g (0.02 mole) of **1** and 1.8 g (0.02 mole) of acetyl chloride in 200 ml of ether in the presence of 30 ml of 2*N* sodium hydroxide solution. The usual workup gave after recrystallization from methanol/water 2.4 g of the product, yield 37%, mp 183-185°; ms: 328 [M+]; nmr: 1.77 (s, 3, CH_3), 2.1-3.5 (m, 5, CH_2CH_2 + NH), 7.0-7.9 (m, 8, arom H), 9.0 (s, 1, NH); ir: 1675, 1705 (C=O) 3450 (NH) cm^{-1}).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$ (328.8): C, 65.7; H, 5.2; N, 8.5. Found: C, 65.5; H, 5.4; N, 8.4.

4-Chloro-*N*-{2-[1-(4-Chlorophenyl)-2,3-dihydro-3-oxo-1*H*-isoindol-1-yl]-ethyl}benzamide (**2b**).

Prepared from 6.4 g (0.02 mole) of **1** and 3.9 g (0.022 mole) of benzoyl chloride gave 6.3 g of the product; yield 74% mp 215-217°; ir (nujol): 1640, 1690 (C=O) 3340 (NH) cm^{-1}.

Anal. Calcd. for $C_{23}H_{18}Cl_2N_2O_2$ (425.3): C, 64.9; H, 4.3; N, 6.6; Cl, 16.7. Found: C, 64.8; H, 4.6; N, 6.9; Cl, 16.4.

N-{2-[1-(4-Chlorophenyl)-2,3-dihydro-3-oxo-1*H*-isoindol-1-yl]ethyl}benzeneacetamide (**2c**).

Prepared from 6.4 g (0.02 mole) of amine **1** and 3.4 g (0.022 mole) phenylacetyl chloride as described above to give 6.7 g of product, yield 83%, mp 197-199°.

Anal. Calcd. for $C_{24}H_{21}ClN_2O_2$ (404.9): C, 71.2; H, 5.2; N, 6.9; Cl, 8.8. Found: C, 71.2; H, 5.1; N, 6.7; Cl, 8.9.

4a-(4-Chlorophenyl)-4,4a-dihydro-1-methylpyrimido[6,1-*a*]isoindol-9(3*H*)-one (**3a**).

A mixture of 6.6 g (0.02 mole) of **2a** and 15 ml of phosphorus oxychloride was heated to reflux for 5 hours, cooled and poured on an ice-cold sodium hydroxide solution. The resulting solid was recrystallized 3 times from ethanol/water to give 2.1 g of the product, yield 34%, mp 198-200°; ms: 310 [M+]; nmr: 1.6-2.3 (m, 1), and 2.8-3.8 (m, 3, CH_2CH_2), 2.77 (s, 3, CH_3), 7.2-8.1 (m, 8, arom H); ir: 1660 (C=N) 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}ClN_2O$ (310.8): C, 69.6; H, 4.9; N, 9.0; Cl, 11.4. Found: C, 69.4; H, 4.9; N, 8.8; Cl, 11.8.

1,4a-Bis(4-Chlorophenyl)-4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-one (**3b**).

A solution of 11.5 g (0.027 mole) of **2b** in 30 ml of phosphorus oxychloride was heated to reflux for 5 hours. The mixture was poured on ice and basified with sodium hydroxide, filtered and recrystallized from methanol/water to give 4.5 g of product, yield 38%, mp 174-176°; ms: 406 [M+]; nmr: 1.4-2.2 (m, 1), and 2.7-3.4 (m, 1), and 3.5-4.0 (m, 2, CH_2CH_2), 7.1-8.0 (m, 12, arom H); ir: 1630 (C=N) 1725 (C=O) cm^{-1}.

Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O$ (406.5): C, 67.8; H, 4.0; N, 6.9; Cl, 17.4. Found: C, 67.5; H, 4.0; N, 6.6; Cl, 17.7.

4a-(4-Chlorophenyl)-4,4a-dihydro-1-phenylmethylpyrimido[6,1-*a*]isoindol-9(3*H*)-one (**3c**).

A solution of 5.7 g (0.014 mole) of **2c** in 15 ml of phosphorus oxychloride was heated to reflux for 5 hours, then poured on ice and basified with sodium hydroxide. The solid was collected and recrystallized from methanol/water to give 2.1 g of the product, yield 38%, mp 153-154°; ms: 386 [M+]; nmr: 1.5-2.3 (m, 1), and 2.7-3.4 (m, 3, NCH_2CH_2), 3.83 and 5.8 (d, 1 each, J = 13 Hz, $PhCH_2$), 6.6-7.6 (m, 12, arom H), 7.7-8.0 (m, 1, arom H); ir: 1650, (C=N) 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{19}ClN_2O$ (386.9): C, 74.5; H, 5.2; N, 7.2; Cl, 9.2. Found: C, 74.5; H, 5.0; N, 7.1; Cl, 9.3.

4a-(4-Chlorophenyl)-4,4a-dihydropyrimido[6,1-*a*]isoindol-9(3*H*)-one (**3d**).

A solution of 15 g (0.05 mole) of **1** in 50 ml of formic acid was heated to reflux for 72 hours. The solvent was evaporated under reduced pressure and the residue was recrystallized from methylene chloride/acetone/hexane to give 5.3 g of product, yield 34%, mp 180-181°; ms: 296 [M+]; nmr: 1.6-2.2 (m, 1), and 2.8-3.7 (m, 3, CH_2CH_2), 7.2-7.7 (m, 7, arom H), 7.8-8.1 (m, 1, arom H), 8.4 (t, 1, J = 2 Hz, NCHN); ir: 1640 (C=N) 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$ (296.8): C, 68.8; H, 4.4; N, 9.4; Cl, 11.9. Found: C, 68.7; H, 4.2; N, 9.6; Cl, 11.7.

4a-(4-Chlorophenyl)-2,3,4,4a-tetrahydropyrimido[6,1-*a*]isoindole-1,9-dione (**4**).

A mixture of 1.4 g (0.005 mole) of free base **1** in 50 ml of benzene was heated to reflux for 5 hours with 50 ml of a 12.5% solution of phosgene in benzene. The solvent was distilled off and the residue was washed with methylene chloride then with water and then recrystallized from methanol/water to give 0.3 g of the product, yield 20%, mp > 330°; ms: 312 [M+]; nmr: 2.0-2.2 (d/t, 1, C4-H), 3.0-3.3 (m, 2, C4-H + C3-H), 3.4-3.6 (m, 1, C3-H), 6.7 (1, NH), 7.2-7.6 (m, 7, arom H), 7.9-8.0 (d, 1, C8-H); ir (nujol): 1670, 1740, 3200 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$ (312.8): C, 65.3; H, 4.2; N, 9.0; Cl, 11.3. Found: 65.0; H, 4.5; N, 8.7; Cl, 11.2.

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